

# INTERNATIONAL SEARCH REPORT

International Application No  
**PCT/EP2004/051522**

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC 7 A61K39/108 A61K39/112 C07K14/25 C07K14/245**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC 7 C07K**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, WPI Data, PAJ, EMBASE**

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| <b>X</b>   | <p><b>SHEORAN ABHINEET S ET AL: "Stx2-specific human monoclonal antibodies protect mice against lethal infection with Escherichia coli expressing Stx2 variants."</b><br/> <b>INFECTION AND IMMUNITY. JUN 2003, vol. 71, no. 6, June 2003 (2003-06), pages 3125-3130, XP002301428</b><br/> <b>ISSN: 0019-9567</b><br/> <b>page 3125, right-hand column, paragraph 2</b><br/> <b>- page 3126, right-hand column, paragraph 5; figure 1</b></p> <p style="text-align: center;">-----<br/>-/--</p> | <b>17</b>             |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

**19 October 2004**

Date of mailing of the international search report

**08/11/2004**

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

**Steffen, P**

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/051522

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | MUKHERJEE JEAN ET AL: "Human Stx2-specific monoclonal antibodies prevent systemic complications of Escherichia coli O157:H7 infection." INFECTION AND IMMUNITY. FEB 2002, vol. 70, no. 2, February 2002 (2002-02), pages 612-619, XP002301429<br>ISSN: 0019-9567<br>page 613 - page 614; figure 1; table 1<br>-----                                       | 17                    |
| X          | MACLEOD D L ET AL: "Purification and characterization of an Escherichia coli Shiga-like toxin II variant." INFECTION AND IMMUNITY. MAY 1990, vol. 58, no. 5, May 1990 (1990-05), pages 1232-1239, XP002301430<br>ISSN: 0019-9567<br>page 1234, left-hand column, paragraph 2 - paragraph 3<br>page 1236, left-hand column, paragraph 2; figure 4<br>----- | 17                    |
| X          | DOWNES F P ET AL: "Affinity purification and characterization of Shiga-like toxin II and production of toxin-specific monoclonal antibodies." INFECTION AND IMMUNITY. AUG 1988, vol. 56, no. 8, August 1988 (1988-08), pages 1926-1933, XP002923370<br>ISSN: 0019-9567<br>page 1927 - page 1930; figure 7<br>-----  | 17                    |
| X          | BELISLE B W ET AL: "Monoclonal antibodies with an expanded repertoire of specificities and potent neutralizing activity for Escherichia coli heat-labile enterotoxin." INFECTION AND IMMUNITY. DEC 1984, vol. 46, no. 3, December 1984 (1984-12), pages 759-764, XP002301431<br>ISSN: 0019-9567<br>page 759 - page 760; table 1<br>-----                  | 17                    |
| X          | BELISLE B W ET AL: "Characterization of monoclonal antibodies to heat-labile enterotoxin encoded by a plasmid from a clinical isolate of Escherichia coli." INFECTION AND IMMUNITY. MAR 1984, vol. 43, no. 3, March 1984 (1984-03), pages 1027-1032, XP002301432<br>ISSN: 0019-9567<br>page 1027 - page 1028; table 1<br>-----                            | 17                    |

-/--

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/051522

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| A          | <p>JEMAL C ET AL: "Analysis of Shiga toxin subunit association by using hybrid A polypeptides and site-specific mutagenesis."<br/>JOURNAL OF BACTERIOLOGY. JUN 1995, vol. 177, no. 11, June 1995 (1995-06), pages 3128-3132, XP000669314<br/>ISSN: 0021-9193<br/>page 3128 - page 3129; tables 1,3</p> <p style="text-align: center;">-----</p>  | 1-17                  |
| A          | <p>MELTON-CELSA ANGELA R ET AL: "Activation of Shiga toxin type 2d (Stx2d) by elastase involves cleavage of the C-terminal two amino acids of the A2 peptide in the context of the appropriate B pentamer"<br/>MOLECULAR MICROBIOLOGY, vol. 43, no. 1, January 2002 (2002-01), pages 207-215, XP002267546<br/>ISSN: 0950-382X<br/>page 208, right-hand column, paragraph 2 - page 210, right-hand column, paragraph 1; figures 1-3</p> <p style="text-align: center;">-----</p>  | 1-17                  |
| A          | <p>RODIGHERO CHIARA ET AL: "Structural basis for the differential toxicity of cholera toxin and Escherichia coli heat-labile enterotoxin. Construction of hybrid toxins identifies the A2-domain as the determinant of differential toxicity"<br/>JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 7, 12 February 1999 (1999-02-12), pages 3962-3969, XP002267547<br/>ISSN: 0021-9258<br/>page 3963, right-hand column, paragraph 3 - page 3964, right-hand column, paragraph 1; figure 1</p> <p style="text-align: center;">-----</p> | 1-17                  |
| A          | <p>MARTIN M ET AL: "Recombinant antigen-enterotoxin A2/B chimeric mucosal immunogens differentially enhance antibody responses and B7-dependent costimulation of CD4(+) T cells."<br/>INFECTION AND IMMUNITY. JAN 2001, vol. 69, no. 1, January 2001 (2001-01), pages 252-261, XP002231728<br/>ISSN: 0019-9567<br/>page 253 - page 255; figure 1</p> <p style="text-align: center;">-----</p>  | 1-17                  |

-/--

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| A          | JOBLING M G ET AL: "Fusion proteins containing the A2 domain of cholera toxin assemble with B polypeptides of cholera toxin to form immunoreactive and functional holotoxin-like chimeras." INFECTION AND IMMUNITY. NOV 1992, vol. 60, no. 11, November 1992 (1992-11), pages 4915-4924, XP002292263<br>ISSN: 0019-9567<br>page 4916 - page 4920<br>----- | 1-17                  |
| A          | WO 01/70945 A (SIBTECH INC)<br>27 September 2001 (2001-09-27)<br>figure 1; examples 1-3<br>-----  | 1-17                  |
| A          | WO 01/89456 A (UNIV TULANE ;CLEMENTS JOHN D (US)) 29 November 2001 (2001-11-29)<br>figure 1; example 6.1<br>-----   | 1-17                  |
| A          | EP 1 057 895 A (LOHMANN ANIMAL HEALTH GMBH) 6 December 2000 (2000-12-06)<br>paragraph '0007!; example 1<br>-----  | 1-17                  |
| A          | MERRITT ETHAN A ET AL: "AB-5 toxins" CURRENT OPINION IN STRUCTURAL BIOLOGY, vol. 5, no. 2, 1995, pages 165-171, XP002267548<br>ISSN: 0959-440X<br>figures 1,2; table 1<br>-----   | 1-17                  |
| A          | PATON J C ET AL: "Pathogenesis and diagnosis of Shiga toxin-producing Escherichia coli infections." CLINICAL MICROBIOLOGY REVIEWS. JUL 1998, vol. 11, no. 3, July 1998 (1998-07), pages 450-479, XP002105349<br>ISSN: 0893-8512<br>page 469, right-hand column, paragraph 3 -<br>page 470, right-hand column, paragraph 3<br>-----                        | 1-17                  |
| A          | LEBENS M ET AL: "Synthesis of hybrid molecules between heat-labile enterotoxin and cholera toxin B subunits: potential for use in a broad-spectrum vaccine." INFECTION AND IMMUNITY. JUN 1996, vol. 64, no. 6, June 1996 (1996-06), pages 2144-2150, XP002301433<br>ISSN: 0019-9567<br>the whole document<br>-----  | 1-17                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/051522

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---|---------------------|----------------------------|---------------------|
| WO 0170945                                | A | 27-09-2001          | US 2001031485 A1           | 18-10-2001          |
|   |   |                     | EP 1268760 A1              | 02-01-2003          |
|   |   |                     | JP 2003533980 T            | 18-11-2003          |
|   |   |                     | WO 0170945 A1              | 27-09-2001          |
|   |   |                     | US 2004166565 A1           | 26-08-2004          |
| -----                                     |   |                     |                            |                     |
| WO 0189456                                | A | 29-11-2001          | AU 7126801 A               | 03-12-2001          |
|   |   |                     | WO 0189456 A2              | 29-11-2001          |
| -----                                     |   |                     |                            |                     |
| EP 1057895                                | A | 06-12-2000          | EP 1057895 A1              | 06-12-2000          |
|   |   |                     | AU 5075200 A               | 28-12-2000          |
|   |   |                     | CN 1357047 T               | 03-07-2002          |
|   |   |                     | WO 0075345 A1              | 14-12-2000          |
|   |   |                     | EP 1183374 A1              | 06-03-2002          |
| -----                                     |   |                     |                            |                     |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2004/051522

## Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of Item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
  - a. type of material
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing
    - ☒ contained in the international application as filed
    - ☐ filed together with the international application in computer readable form
    - ☐ furnished subsequently to this Authority for the purpose of search
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments: